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FIELD OF THE INVENTION

The present invention relates to new compounds, to pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of said compounds.

BACKGROUND OF THE INVENTION

Pain sensation in mammals is due to the activation of the peripheral terminals of a specialized population of sensory neurons known as nociceptors. Capsaicin, the active ingredient in hot peppers, produces sustained activation of nociceptors and also produces a dose-dependent pain sensation in humans. Cloning of the vanilloid receptor 1 (VR1 or TRPV1) demonstrated that VR1 is the molecular target for capsaicin and its analogues. (Caterina,M.J., Schumacher,M.A., et.al. Nature 1997 v.389 p 816-824). Functional studies using VR1 indicate that it is also activated by noxious heat and that the threshold for activation can be lowered below normal body temperature by a reduction of the extracellular pH value (acidification) and by other inflammatory mediators Tominaga,M., Caterina,M.J. et.al. Neuron 1998 v.21, p.531-543). Expression of VR1 is also regulated after peripheral nerve damage of the type that leads to neuropathic pain. These properties of VR1 make it a highly relevant target for pain and for diseases involving inflammation. Agonists of the VR1 receptor can act as analgesics, but the usefulness of agonists, such as capsaicin and its analogues, is limited by their pungency, neurotoxicity and induction of hypothermia. Pain-evoking stimuli activate the VR1 receptor and agents that block the activity of VR1 have also shown analgesic activity in animals.

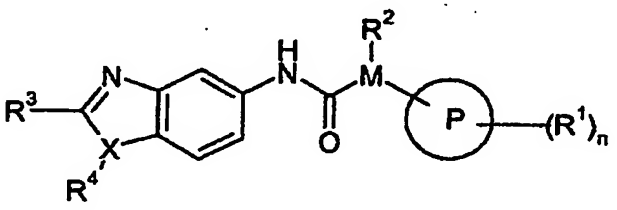
Compounds with VR1 blocker activity are believed to be of potential use for the treatment or prophylaxis of disorders such as pain, especially that of inflammatory or traumatic origin such as arthritis, fibromyalgia, low back pain and post-operative pain. (Walker et al J Pharmacol Exp Ther. 2003 Jan; 304(1):56-62), or visceral pains such as chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis and the like, and also neuropathic pain such as sciatia, diabetic neuropathy and HIV neuropathy, and the like

(Walker et al *ibid*, Rashid et al J Pharmacol Exp Ther. 2003 Mar;304(3):940-8). These compounds are also believed to be potentially useful for inflammatory disorders like asthma, cough, inflammatory bowel disease (IBD) (Hwang and Oh Curr Opin Pharmacol 2002 Jun; 2(3):235-42). Compounds with VR1 blocker activity are also useful for itch and skin diseases like psoriasis and for gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder (Yiangou et al BJU Int 2001 Jun; 87(9): 774-9, Szallasi Am J Clin Pathol 2002 118: 110-21). VR1 inhibitors are also of potential use for the treatment or prophylaxis of the effects of exposure to VR1 activators like capsaicin or tear gas, acids or heat (Szallasi *ibid*).

DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is to provide compounds exhibiting an activity at the vanilloid receptor 1 (VR1).

The present invention provides a compound of formula I



wherein:

ring P is C_{6-10}aryl, C_{3-7}cycloalkyl, C_{5-6}heteroaryl, whereby ring P may be fused with phenyl, C_{5-6}heteroaryl, C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl;

R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, phenylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl or C_{1-6}alkylNC_{0-6}alkyl;

n is 1, 2, 3 or 4;

M is C_{0-4}alkyl, C_{1-6}alkylNC_{0-6}alkyl, N or O;

R^2 is H or C_{0-4}alkyl;

R^3 is H, C_{1-6}alkyl, halo, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, CR^5O, CO_2R^5, $CONR^5R^6$ or NR^5R^6;

X is N, O or S;

R^4 is H or C_{0-4}alkyl;

R^5 and R^6 are independently selected from H and C_{1-4}alkyl;

and wherein any alkyl, alkylOalkyl, haloalkyl, haloalkylO, phenyl, heteroaryl, cycloalkyl or heterocycloalkyl group may be substituted with one or more A; and

A is OH, NO_2, NH_2, CO, O(CO) or halo;

or salts, solvates or solvated salts thereof.

One embodiment of the invention relates to the compound of formula I wherein ring P is C_{6-10}aryl or C_{5-6}heteroaryl, whereby ring P may be fused with phenyl or C_{3-7}heterocycloalkyl;

R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, OC_{1-6}haloalkyl, phenylC_{0-6}alkyl, C_{0-6}alkylOC_{1-6}alkyl or C_{0-6}alkylSC_{1-6}alkyl;

n is 1, 2 or 3;

M is C_{0-4}alkyl, C_{0-4}alkylNH or N;

R^2 is H or C_{0-4}alkyl;

R^3 is C_{1-6}alkyl or C_{1-6}haloalkyl;

R^4 is H or C_{1-4}alkyl;

X is N, O or S; and

A is OH, NO_2, NH_2 or halo.

Another embodiment of the invention relates to the compound of formula I wherein ring P is C_{6-10}aryl and R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, phenylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl or C_{1-6}alkylNC_{0-6}alkyl.

A further embodiment of the invention relates to the compound of formula I wherein ring P is C_{5-6}heteroaryl and R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, phenylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl or C_{1-6}alkylNC_{0-6}alkyl.

Yet another embodiment of the invention relates to the compound of formula I wherein ring P is C_{6-10}aryl fused with phenyl, C_{5-6}heteroaryl, C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl and
R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, phenylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl or C_{1-6}alkylNC_{0-6}alkyl.

Yet a further embodiment of the invention relates to the compound of formula I wherein ring P is phenyl, pyrazole, pyridine, furan or thiophene.

Ring P may be substituted with 0, 1, 2, 3, or 4 substituents R^1 wherein the number of substituents is designated by the term n. The substituent R^1 is selected from the group consisting of H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, phenylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl and C_{1-6}alkylNC_{0-6}alkyl.
In one embodiment of the invention R^1 is elected from the group consisting of H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, OC_{1-6}haloalkyl, phenylC_{0-6}alkyl, C_{0-6}alkylOC_{1-6}alkyl and C_{0-6}alkylSC_{1-6}alkyl and n is 0, 1, or 2.
Ring P may be substituted by R^1 on a nitrogen or carbon atom in ring P. Further, one atom on ring P may be substituted by two substituents R^1.

M is selected form the group consisting of C_{0-4}alkyl, C_{0-4}alkylNH and N. In one embodiment of the invention M is a direct bond between C=O and ring P. In another embodiment of the invention M is N or O. In yet another embodiment of the invention M is

C_{1-2}alkyl or C_{1-2}alkylN.

M may be substituted by substituent R^2. In one embodiment R^2 is H when M is N or alkyl.

R^3 may be selected from the group consisting of H, C_{1-6}alkyl, halo, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, CR^5O, CO_2R^5, $CONR^5R^6$ and NR^5R^6 whereby R^5 and R^6 are independently selected from H and C_{1-4}alkyl.
In one embodiment of the invention R^3 is selected form the group consisting of C_{1-6}alkyl and C_{1-6}haloalkyl.
Another embodiment of the invention relates to the compound of formula I wherein R^3 is methyl.

X may be selected from the group consisting of N, O and S. X may be substituted with R^4 when X is N. One embodiment of the invention relates to compounds of formula I wherein X is N and R^4 is H or C_{1-4}alkyl. In another embodiment of the invention X is N and R^4 is H or C_{1-2}alkyl.

Any alkyl, alkylOalkyl, haloalkyl, haloalkylO, phenyl, heteroaryl, cycloalkyl or heterocycloalkyl group present in the substituents of the compounds of formula I may be substituted with one or more A. One embodiment of the invention relates to compounds of formula I wherein A is selected from the group consisting of OH, NO_2, NH_2, CO, O(CO) and halo.

Another embodiment of the invention relates to compounds selected from the group consisting of 3-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide,
2-tert-Butyl-5-methyl-2*H*-pyrazole-3 -carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,
2-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide,
2-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-3-trifluoromethyl-benzamide,
4-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-3-trifluoromethyl-benzamide,
3,4-Dimethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid (2-methylbenzothiazol-5-yl)-amide,
N-(2-Methyl-benzothiazol-5-yl)-6-trifluoromethyl-nicotinamide,

N-(2-Methyl-benzothiazol-5-yl)-4-propyl-benzamide,

3-Iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

2,5-Dimethyl-furan-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

N-(2-Methyl-benzothiazol-5-yl)-3-phenyl-propionamide,

5-tert-Butyl-2-methyl-furan-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

4-Bromo-3-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

3,4-Difluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

3-Chloro-2-fluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

Pyridine-2-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

2-Benzyl-5-tert-butyl-2*H*-pyrazole-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

3-Fluoro-4-trifluoromethyl-*N*-(2-trifluoromethyl-1*H*-benzoimidazol-5-yl)-benzamide,

2-Fluoro-5-trifluoromethyl-*N*-(2-trifluoromethyl-1*H*-benzoimidazol-5-yl)-benzamide,

4-Chloro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

1-Phenyl-5-trifluoromethyl-1*H*-pyrazole-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

1-Phenyl-5-propyl-1*H*-pyrazole-4-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

2,3-Difluoro-*N*-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide,

3-Fluoro-4-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

4-tert-Butyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

4-Ethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

N-[1-(2-hydroxyethyl)-2-methyl-1*H*-benzimidazol-5-yl]-*N'*-(4-methoxyphenyl)urea,

N-(3,5-dimethoxyphenyl)-*N'*-[1-(2-hydroxyethyl)-2-methyl-1*H*-benzimidazol-5-yl]urea,

2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-benzothiazol-5-yl)-acetamide,

4-tert-Butyl-*N*-(2-methyl-benzooxazol-5-yl)-benzamide,

Biphenyl-4-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

3-Bromo-thiophene-2-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

4-Bromo-2-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

4-tert-Butoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

2-Chloro-3,4-dimethoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

4-Iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

4-Amino-*N*-(2-methyl-benzothiazol-5-yl)-3-nitro-benzamide,

N-(2-Methyl-benzothiazol-5-yl)-4-vinyl-benzamide,

4-Ethoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-Ethylsulfanyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-Dimethylamino-naphthalene-1-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,
2-Fluoro-6-iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-Ethoxymethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
N-(2-Methyl-benzothiazol-5-yl)-4-trifluoromethoxy-benzamide, and
4-Chloro-3-fluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide.
or salts, solvates or solvated salts thereof.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl. The term C_{1-3} alkyl having 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl, i-propyl or *tert*-butyl.

The term 'C_0' means a bond or does not excist. For example when M is C_0alkyl, M is a bond and "arylC_0alkyl" is equivalent with "aryl", "C_2aklylOC_0alkyl" is equivalent with "C_2alkylO".

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups. The term "C_{2-6}alkenyl" having 2 to 6 carbon atoms and

one or two double bonds, may be, but is not limited to vinyl, allyl, propenyl, butenyl, crotyl, pentenyl, or hexenyl, and a butenyl group may for example be buten-2-yl, buten-3-yl or buten-4-yl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups. The term "C_{2-6}alkynyl" having 2 to 6 carbon atoms and one or two trippel bonds, may be, but is not limited to etynyl, propargyl, pentynyl or hexynyl and a butynyl group may for example be butyn-3-yl or butyn-4-yl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C_{3-7}cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocycloalkyl" denotes a 3- to 7-membered, non-aromatic, partially or completely saturated hydrocarbon group, which contains one rings and at least one heteroatom. Examples of said heterocycle include, but are not limited to pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, piperazinyl, morpholinyl, oxazolyl, 2-oxazolidonyl or tetrahydrofuranyl.

In this specification, unless stated otherwise, the term "aryl" refer to an optionally substituted monocyclic or bicyclic hydrocarbon unsaturated aromatic ring system. Examples of "aryl" may be, but are not limited to phenyl and naphthyl.

In this specification, unless stated otherwise, the term "heteroaryl" refer to an optionally substituted monocyclic or bicyclic unsaturated aromatic ring system containing at least one heteroatom selected independently form N, O or S. Examples of "heteroaryl" may be, but are not limited to pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl and oxazolyl.

In this specification, unless stated otherwise, the term "arylalkyl" and "heteroarylalkyl" refer to a substituent that is attached via the alkyl or group to an aryl group.

In this specification, unless stated otherwise, the term "halo" and "halogen" may be fluoro, iodo, chloro or bromo.

In this specification, unless stated otherwise, the term "haloalkyl" means an alkyl group as defined above, which is substituted with halo as defined above. The term "C_{1-6}haloalkyl" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term "C_{1-6}haloalkylO" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts, solvates or solvated salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18th Edition, Mack Publishing Co.).

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

The invention also relates to any and all tautomeric forms of the compounds of formula I.

Methods of Preparation

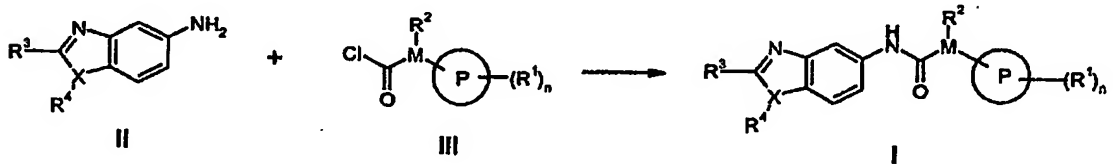
Another aspect of the present invention provides processes for preparing compounds of formula I, or salts, solvates or solvated salts thereof.

Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). For representative examples of heterocyclic chemistry see for example "Heterocyclic Chemistry", J. A. Joule, K. Mills, G. F. Smith, 3rd ed. Chapman and Hall (1995), p. 189-224 and "Heterocyclic Chemistry", T. L. Gilchrist, 2nd ed. Longman Scientific and Technical (1992), p. 248-282.

The term "room temperature" and "ambient temperature" shall mean, unless otherwise specified, a temperature between 16 and 25 °C.

One embodiment of the invention relates to processes for the preparation of the compound of formula I according to Methods A and B, wherein R^1 to R^4, unless otherwise specified, are defined as in formula I, comprising;

Method A



II + III → I

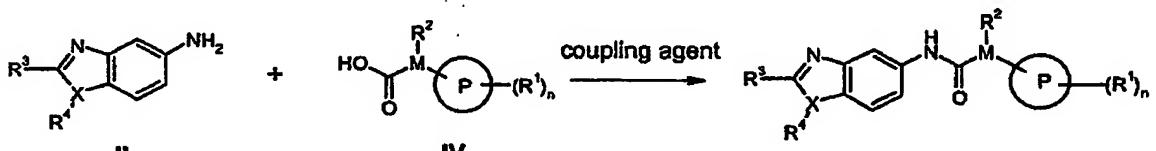
whereby the amide of formula I is obtained from the amine of formula II and an appropriate acyl chloride of formula III.

This reaction may be performed in any manner known to the skilled person in the art.

Suitable solvents to be used for this reaction may be halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxan or any mixtures thereof. Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well. The temperature may be between -40 and 40°C and the reaction time may be between 0.5 and 30 h.

Or,

Method B



II IV I

whereby the amide of formula I is obtained from the amine of formula II and an appropriate carboxylic acid of formula IV in the presence of a coupling agent like for example 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

This reaction may be performed in any manner known to the skilled person in the art. Suitable solvents to be used for this reaction may be tertiary amides such as dimethylformamide and dimethylacetamide, halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxan or any mixtures thereof. Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well. The temperature may be between 10 and 60°C and the reaction time may be between 3 and 30 h.

Pharmaceutical formulation

According to one aspect of the present invention there is provided a pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, or salts, solvates or solvated salts thereof, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.

In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers. Suitable daily doses of the compound of formula I in the treatment of a mammal, including man are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound being used, and may be determined by a physician.

Medical use

Surprisingly, it has been found that the compounds according to the present invention are useful in therapy. The compounds of formula I, or salts, solvates or solvated salts thereof, as well as their corresponding active metabolites, exhibit a high degree of potency and selectivity for individual vanilloid receptor 1 (VR1) groups. Accordingly, the compounds of the present invention are expected to be useful in the treatment of conditions associated with excitatory activation of vanilloid receptor 1 (VR1).

The compounds may be used to produce an inhibitory effect of VR1 in mammals, including man.

VR1 are highly expressed in the peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of VR1 mediated disorders. The compounds of formula I are expected to be suited for the treatment of acute and chronic pain and acute and chronic inflammatory pain. The compound may further be suited for the treatment of chronic neuropathic pain.

Examples of such disorder may be selected from the group comprising of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, inflammatory bowel disease (IBD) and psoriasis.

Further relevant disorders that may be treated using the compounds of formula I may be selected from the group comprising of gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

The compounds of formula I may also be used as antitoxin to treat (over-) exposure to VR1 activators like capsaicin or tear gas, acids or heat.

The compounds may further be used for treatment of tolerance to VR1 activators.

One embodiment of the invention relates to the use of the compound of formula I in therapy.

Another embodiment of the invention relates to the use of the compound of formula I for treatment of VR1 mediated disorders.

A further embodiment of the invention relates to the use of the compound of formula I for treatment of acute and chronic pain disorders

Yet another embodiment of the invention relates to the use of the compound of formula I for treatment of acute and chronic inflammatory pain.

Yet a further embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, for treatment of indications selected form the group consisting of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, IBS, pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, IBD, psoriasis, gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

One embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, as hereinbefore defined.

A further embodiment of the invention relates to a pharmaceutical formulation comprising the compound of formula I, as hereinbefore defined, for use in the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain and any other disorder mentioned above.

In the context of the present specification, the term "therapy" and "treatment" includes prevention and prophylaxis, unless there are specific indications to the contrary. The terms "treat","therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term "antagonist" and "inhibitor" mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

The term "disorder", unless stated otherwise, means any condition and disease associated with vanilloid receptor activity.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of formula I, or salts, solvates or solvated salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of VR1 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Examples

The invention will now be illustrated by the following non-limiting examples.

General methods

All starting materials are commercially available or described in the literature. The ^1H NMR spectra were recorded on Brucker at 400 MHz. The mass spectra were recorded utilising electrospray (LC-MS; LC:Waters 2790, column XTerra MS C_8 2.5 μm 2.1X30 mm, buffer gradient H_2O+0.1%TFA:CH_3CN+0.04%TFA, MS: micromass ZMD// ammonium acetate buffer) ionisation techniques.

Example 1

3-Fluoro-N-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide

A solution of 3-fluoro-4-trifluoromethyl-benzoyl chloride (8.2 mg, 0.036 mmol) in anhydrous dioxane (0.5 mL) and a solution of 2-methyl-benzothiazol-5-ylamine (5.3 mg, 0.030 mmol) in anhydrous dioxane (0.5 mL) were added to a suspension of *N,N*-(diisopropyl)aminomethylpolystyrene resin (50 mg, Argonaut Technologies, Inc) in dichloromethane (0.5 mL). The reaction was shaken overnight at room temperature. Water (0.01 mL) and DOWEX 550A OH (50 mg) were added and the reaction mixture was

shaken for an additional 1 h. The resins were filtered off and the solvent was evaporated to afford the title compound (9.6 mg, 90 %).
MW found [M+1]: 354.04

The compounds shown in Table 1 (Examples 2-20) were prepared according to the procedure described in Example 1 using 2-methyl-benzothiazol-5-ylamine and an appropriate commercially available acid chlorides.

Table 1

Example number	Name	MW calcd	MW found [M+1]
2	2-tert-Butyl-5-methyl-2*H*-pyrazole-3 -carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	328.44	329
3	2-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide	354.33	355
4	2-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-3-trifluoromethyl-benzamide	354.33	355
5	4-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-3-trifluoromethyl-benzamide	354.33	355
6	3,4-Dimethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	296.39	297.1
7	2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid (2-methylbenzothiazol-5-yl)-amide	348.33	349

8	*N*-(2-Methyl-benzothiazol-5-yl)-6-trifluoromethyl-nicotinamide	337.32	338
9	*N*-(2-Methyl-benzothiazol-5-yl)-4-propyl-benzamide	310.42	311.1
10	3-Iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	394.23	394.9
11	2,5-Dimethyl-furan-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	286.35	287
12	*N*-(2-Methyl-benzothiazol-5-yl)-3-phenyl-propionamide	296.39	297.1
13	5-tert-Butyl-2-methyl-furan-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	328.43	329.1
14	4-Bromo-3-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	361.26	360.99
15	3,4-Difluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	304.32	305
16	3-Chloro-2-fluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	320.77	321
17	Pyridine-2-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	269.33	270
18	2-Benzyl-5-tert-butyl-2*H*-pyrazole-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	404.54	405.1
19	3-Fluoro-4-trifluoromethyl-*N*-(2-trifluoromethyl-1*H*-benzoimidazol-5-yl)-benzamide	391.25	392

20	2-Fluoro-5-trifluoromethyl-*N*-(2-trifluoromethyl-1*H*-benzoimidazol-5-yl)-benzamide	391.25	392

Example 21

4-Chloro-N-(2-methyl-benzothiazol-5-yl)-benzamide

4-Chloro-benzoyl chloride (102 mg, 0.58 mmol) was added to a solution of triethylamine (49 mg, 0.49 mmol) and 2-methyl-benzothiazol-5-ylamine (80 mg, 0.49 mmol) in anhydrous dioxane (5 mL). The reaction mixture was stirred at room temperature overnight and the solvent evaporated. The crude product was purified on a preparative HPLC (XTerra C8 column 19x300 mm, 0.1 M aqueous NH_4Ac/CH_3CN). Product-containing fractions were pooled and lyophilized to afford 104 mg (70 %) of the title compound.
MW found [M+1]: 302.88
1H NMR (400 MHz, DMSO-D6) δ ppm 2.8 (s, 3 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.8 (d, *J*=9.1 Hz, 1 H) 8.0 (m, 3 H) 8.4 (s, 1 H) 10.5 (s, 1 H)

The compounds shown in Table 2 (Examples 22-26) were prepared according to a procedure described in Example 21 using 2-methyl-benzothiazol-5-ylamine and an appropriate commercially available acid chlorides.

Table 2

Example number	Name	Yield	MW calcd	MW found [M+1]	NMR
22	1-Phenyl-5-trifluoromethyl-1*H*-pyrazole-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	135 mg (69%)	402.40	402.89	1H NMR (400 MHz, DMSO-D6) δ ppm 2.8 (s, 3 H) 7.5 (m, 2 H) 7.6 (m, 3 H) 7.7 (d, *J*=9.1 Hz, 1 H) 8.0 (d, *J*=8.6 Hz, 1 H) 8.3 (m, 2 H) 10.7 (s, 1 H)
23	1-Phenyl-5-propyl-1*H*-pyrazole-4-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	22 mg (12%)	376.48	376.92	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.8 (t, *J*=7.3 Hz, 3 H) 1.5 (m, 2 H) 2.8 (s, 3 H) 2.9 (m, 2 H) 7.4 (m, 2 H) 7.4 (m, 3 H) 7.7 (s, 1 H) 7.7 (m, 2 H) 7.9 (s, 1 H) 8.0 (m, 1 H)
24	2,3-Difluoro-*N*-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide	11 mg (13%)	372.32	372.74	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.8 (s, 3 H) 7.5 (t, *J*=7.3 Hz, 1 H) 7.7 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.8 (d, *J*=8.6 Hz, 1 H) 8.0 (t, *J*=7.6 Hz, 1 H) 8.2 (d, *J*=2.0 Hz, 1 H) 8.4 (d, broad, 1 H)

25	3-Fluoro-4-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	71 mg (92%)	300.36	300.76	
26	4-tert-Butyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	55 mg (15%)	324.45	325.16	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.4 (s, 9 H) 2.8 (s, 3 H) 7.5 (d, *J*=8.6 Hz, 2 H) 7.8 (m, 2 H) 7.8 (d, *J*=8.6 Hz, 2 H) 7.9 (s, 1 H) 8.1 (m, 1 H)
27	4-Ethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide		296.39	297.15	

Example 28

N-[1-(2-hydroxyethyl)-2-methyl-1H-benzimidazol-5-yl]-N'-(4-methoxyphenyl)urea

To a solution of 2-(5-amino-2-methyl-1*H*-benzimidazol-1-yl)ethanol (5.74 mg, 0.030 mmol) in a mixture of 1,4-dioxane and dimethyl sulfoxide (1:1 by volume, 1.2 ml) a solution of 4-methoxyphenyl isocyanate (4.47 mg, 0.030 mmol) in dry 1,4-dioxane (0.067 ml) was added under inert atmosphere at room temperature. After shaking at room temperature for 18 h the reaction mixture was left for an additional 7 days without shaking. A mixture of THF and DMSO was added to dissolve the precipitated product. Polymer bound isocyanate and polymer bound amine were added and the reaction mixture was shaken for 20 h at room temperature. The product was separated from the polymer bound scavengers by filtration and the solvents were removed, using a heated nitrogen (40°C) gas flow, to give the title compound (2.5 mg, 25%). MW found [M+1]: 341.1

Example 29

N-(3,5-dimethoxyphenyl)-N'-[1-(2-hydroxyethyl)-2-methyl-1H-benzimidazol-5-yl]urea

The title compounds was synthesized in 27% yield according to the procedure described in Example 28 starting from 2-(5-amino-2-methyl-1*H*-benzimidazol-1-yl)ethanol and 3,5-dimethoxyphenyl isocyanate. MW found [M+1]: 371.1

Example 30

2-(3,4-Difluoro-phenylamino)-N-(2-methyl-benzothiazol-5-yl)-acetamide

2-Methyl-benzothiazol-5-ylamine (32 mg, 0.2 mmol) and bromoacethyl bromide were added to a suspension of *N,N*-diisopropyl)aminomethylpolystyrene resin (170 mg) in anhydrous THF (2 mL) and the reaction was shaken for 4 h at room temperature. The resin was filtrated off. 3,4-Difluoro-phenylamine (39 mg, 0.3 mmol) and potassium iodide (5 mg, 0.03 mmol) were added and the mixture was shaken at 55 °C for 24 h. The crude product was purified on a preparative LC/MS (XTerra C8 column 19x100 mm, 0.1 M aqueous NH_4Ac/CH_3CN). The product was lyophilized to afford 1.4 mg (2 %) of the title compound.

MW found [M+1]: 334.0, 1H NMR (400 MHz, MeOH) δ ppm 2.8 (s, 3 H) 3.9 (s, 2 H) 6.4 (m, 1 H) 6.5 (m, 1 H) 7.0 (m, 1 H) 7.5 (dd, *J*=8.6, 2.0 Hz, 1 H) 7.8 (d, *J*=8.6 Hz, 1 H) 8.3 (d, *J*=2.0 Hz, 1 H)

Example 31

4-tert-Butyl-N-(2-methyl-benzooxazol-5-yl)-benzamide

To a solution of 2-Methyl-benzothiazol-5-ylamine (15 mg, 0.1 mmol) in dichloromethane (0.5 ml) containing triethylamine (12 mg, 0.12 mmol) a solution of 4-tert-butyl-benzoyl chloride (23 mg, 0.12 mmol) in dichloromethane (0.5 ml) was added at 5°C. The mixture was stirred at room temperature for 2 h. The organic layer was washed with water and a saturated solution of sodium bicarbonate, then dried over anhydrous sodium sulphate and finally concentrated to leave the title product (24 mg, 78%). MW found [M+1]: 309

Example 32

Biphenyl-4-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide

Biphenyl-4-carboxylic acid (19.8 mg, 0.1 mmol) was dissolved in dimethylformamide (1 mL). A solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.1 mmol), 4-(dimethylamino)-pyridine (0.1 mmol) and 5-amino-2-methylbenzothiazole (0.06 mmol) in a mixture of dimethylformamide (0.5 mL) and dichloroethane (0.5 mL) was added to the solution of the acid. After the mixture was stirred for 18 h, the solvents were removed by evaporation under reduced pressure. The residue was dissolved in ethyl acetate (1 mL) and washed with 1 N sodium hydroxide (1 mL) followed by 1 N hydrochloric acid (1 mL). The organic phase was reduced to dryness by evaporation under reduced pressure to yield the title product (23 mg, 67%). MW found [M+1]: 345

The compounds shown in Table 3 (Examples 33-46) were prepared according to a procedure described in Example 32 starting from 2-methyl-benzothiazol-5-ylamine and an appropriate commercially available carboxylic acids.

Table 3

Example number	Name	MW calcd	MW found [M+1]	NMR
33	3-Bromo-thiophene-2-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	353.26	354	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.84 (s, 3 H) 7.11 (d, *J*=5.27 Hz, 1 H) 7.54 (d, *J*=5.27 Hz, 1 H) 7.73 (dd, *J*=8.79, 2.15 Hz, 1 H) 7.80 (d, *J*=8.59 Hz, 1 H) 8.20 (d, *J*=1.95 Hz, 1 H) 8.98 (s, 1 H)

34	4-Bromo-2-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	361.26	362	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.50 (s, 3 H) 2.84 (s, 3 H) 7.42 (d, *J*=19.14 Hz, 2 H) 7.64 (s, 1 H) 7.77 (m, 3 H) 8.10 (s, 1 H)
35	4-tert-Butoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	340.45	341	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.41 (m, 9 H), 2.84 (s, 3 H), 7.09 (d, *J*=8.79 Hz, 2 H), 7.78 (m, 2 H), 7.83 (d, *J*=8.98 Hz, 2 H), 7.93 (s, 1 H), 8.12 (m, 1 H)
36	2-Chloro-3,4-dimethoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	362.84	363	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.84 (s, 3 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 6.94 (d, *J*=8.79 Hz, 1 H), 7.62 (d, *J*=8.79 Hz, 1 H), 7.78 (m, 2 H), 8.18 (s, 1 H).
37	4-Iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	394.24	395	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.84 (s, 3 H) 7.64 (d, *J*=8.59 Hz, 2 H) 7.73 (dd, *J*=8.59, 1.95 Hz, 1 H) 7.80 (m, 1 H) 7.86 (d, *J*=8.59 Hz, 2 H) 7.94 (m, 1 H) 8.14 (d, *J*=1.95 Hz, 1 H)

38	4-Amino-*N*-(2-methyl-benzothiazol-5-yl)-3-nitro-benzamide	328.35	329	1H NMR (400 MHz, DMSO-D6) δ ppm 2.79 (s, 3 H), 7.10 (d, *J*=8.98 Hz, 1 H), 7.75 (m, 1 H), 7.87 (s, 2 H), 7.96 (d, *J*=8.59 Hz, 1 H), 8.01 (dd, *J*=8.89, 2.25 Hz, 1 H), 8.39 (m, 1 H), 8.75 (d, *J*=2.15 Hz, 1 H), 10.37 (s, 1 H)
39	*N*-(2-Methyl-benzothiazol-5-yl)-4-vinyl-benzamide	294.38	295	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.84 (s, 3 H) 5.40 (d, *J*=10.94 Hz, 1 H) 5.87 (d, *J*=17.57 Hz, 1 H) 6.78 (dd, *J*=17.57, 10.94 Hz, 1 H) 7.52 (d, *J*=8.20 Hz, 2 H) 7.78 (m, 2 H) 7.87 (d, *J*=8.40 Hz, 2 H) 7.99 (s, 1 H) 8.15 (s, 1 H)
40	4-Ethoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	312.39	313	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.45 (t, *J*=7.03 Hz, 3 H) 2.83 (s, 3 H) 4.10 (q, *J*=14.06, 7.03 Hz, 2 H) 6.96 (d, *J*=8.98 Hz, 2 H) 7.77 (m, 2 H) 7.88 (d, *J*=6.83 Hz, 2 H) 7.98 (s, 1 H) 8.11 (m, 1 H)

41	4-Ethylsulfanyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	328.46	329	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.37 (t, *J*=7.42 Hz, 3 H) 2.83 (s, 3 H) 3.02 (q, *J*=14.65, 7.22 Hz, 2 H) 7.33 (d, *J*=8.79 Hz, 2 H) 7.76 (s, 2 H) 7.81 (d, *J*=8.59 Hz, 2 H) 8.13 (s, 2 H)
42	4-Dimethylamino-naphthalene-1-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide	361.47	362	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.85 (s, 3 H), 2.96 (m, 6 H), 7.03 (d, *J*=7.81 Hz, 1 H), 7.54 (m, 2 H), 7.72 (d, *J*=7.81 Hz, 1 H), 7.83 (m, 3 H), 8.13 (m, 1 H), 8.26 (m, 1 H), 8.43 (m, 1 H).
43	2-Fluoro-6-iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	412.23	413	
44	4-Ethoxymethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	326.42	327	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.27 (t, *J*=14.06, 7.03 Hz, 3 H) 2.84 (s, 3 H) 3.58 (q, *J*=14.06, 7.03 Hz, 2 H) 4.58 (s, 2 H) 7.47 (d, *J*=8.59 Hz, 2 H) 7.78 (m, 2 H) 7.88 (d, *J*=8.40 Hz, 2 H) 8.05 (s, 1 H) 8.14 (s, 1 H)

45	*N*-(2-Methyl-benzothiazol-5-yl)-4-trifluoromethoxy-benzamide	352.34	353	1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.84 (s, 3 H) 7.33 (d, *J*=8.79 Hz, 2 H) 7.77 (m, 2 H) 7.95 (d, *J*=8.98 Hz, 2 H) 8.00 (s, 1 H) 8.14 (d, *J*=1.95 Hz, 1 H)
46	4-Chloro-3-fluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide	320.78	321	1H NMR (400 MHz, DMSO-D6) δ ppm 2.74 (s, 3 H), 7.70 (m, 1 H), 7.75 (m, 1 H), 7.82 (dd, *J*=8.40, 1.95 Hz, 1 H), 7.96 (m, 2 H), 8.266 (m, 1 H), 10.49 (s, 1 H)

Pharmacology

DRGs were dissected out from adult Sprague Dawley rats (100-300 gr), and placed on ice in L15 Leibovitz medium. The ganglia were enzyme treated with Collagenase 80U/ml+ Dispase 34 U/ml dissolved in DMEM +5% serum, overnight at 37 °C. The next day, cells were triturated with fire polished pasteur pipettes, and seeded in the center of 58 mm diameter Nunc cell dishes coated with Poly-D Lysine (1 mg/mL). The DRGs were cultured in a defined medium without foetal bovine serum, containing Dulbecco's MEM / NUT MIX F-12 (1:1) without L-glutamine but with pyridoxine, 6 mg/mL D(+)-Glucose, 100 µg/mL apo-transferrin, 1 mg/mL BSA, 20 µg/mL insulin, 2 mM L-glutamine, 50 IU/ mL Penicillin, 50 µg / mL Streptomycin and 0.01 µg/mL NGF-7S.

When the cells had grown for 2 days up to 4 weeks, the experiments were done. Cells were chosen based on size and presence of neurites. Small cells with long processes were used for recording (most likely to be C neurons, with native VR1 receptors).

The cells were recorded with conventional whole cell voltage clamp patch clamp, using the following solutions (calcium ion free):

The extracellular solution comprised (in mM): NaCl 137, KCl 5, $MgCl_2$ * H_2O 1.2, HEPES 10, Glucose 10, EGTA 5, Sucrose 50, pH to 7.4 with NaOH.
The intracellular solution comprised K-gluconate 140, NaCl 3, $MgCl_2$ * H_2O 1.2, HEPES 10, EGTA 1, pH to 7.2 with KOH. When the cells were penetrated with suction, a puff of capsaicin (500 nM) was used to determine if the cell expressed VR1 receptor. If not, a new cell was chosen. If yes, then the compounds were added in increasing doses before the capsaicin pulse (500 nM), to determine an IC_{50} value.

List of abbreviations

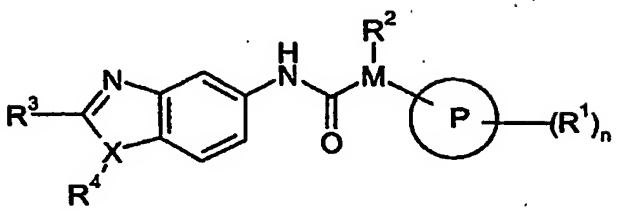
VR1	vanilloid receptor 1
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
GERD	gastro-esophageal reflux disease
DRG	Dorsal Root Ganglion
BSA	Bovine Serum Albumin
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
EGTA	Ethylene glycol-bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid
DMEM	Dulbeccos Modified Eagle's Medium

Results

Typical IC_{50} values as measured in the assays described above are 10 μM or less. In one aspect of the invention the IC_{50} is below 500 nM. In another aspect of the invention the IC_{50} is below 100 nM. In a further aspect of the invention the IC_{50} is below 10 nM.

CLAIMS

1. A compound having the formula I



§ (I)

wherein:

ring P is C_{6-10}aryl, C_{3-7}cycloalkyl, C_{5-6}heteroaryl, whereby ring P may be fused with phenyl, C_{5-6}heteroaryl, C_{3-7}cycloalkyl or C_{3-7}heterocycloalkyl;

R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, phenylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl or C_{1-6}alkylNC_{0-6}alkyl;

n is 1, 2, 3 or 4;

M is C_{0-4}alkyl, C_{1-6}alkylNC_{0-6}alkyl, N or O;

R^2 is H or C_{0-4}alkyl;

R^3 is H, C_{1-6}alkyl, halo, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{1-6}alkylOC_{0-6}alkyl, CR^5O, CO_2R^5, $CONR^5R^6$ or NR^5R^6;

X is N, O or S;

R^4 is H or C_{0-4}alkyl;

R^5 and R^6 are independently selected from H and C_{1-4}alkyl;

and wherein any alkyl, alkylOalkyl, haloalkyl, haloalkylO, phenyl, heteroaryl, cycloalkyl or heterocycloalkyl group may be substituted with one or more A; and

A is OH, NO_2, NH_2, CO, O(CO) or halo;

or salts, solvates or solvated salts thereof.

2. The compound according to claim 1 wherein ring P is C_{6-10}aryl or C_{5-6}heteroaryl, whereby ring P may be fused with phenyl or C_{3-7}heterocycloalkyl;

R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}haloalkyl$, $OC_{1-6}haloalkyl$, $phenylC_{0-6}alkyl$, $C_{0-6}alkylOC_{1-6}alkyl$ or $C_{0-6}alkylSC_{1-6}alkyl$;
n is 1, 2 or 3;
M is $C_{0-4}alkyl$, $C_{0-4}alkylNH$ or N;
R^2 is H or $C_{0-4}alkyl$;
R^3 is $C_{1-6}alkyl$ or $C_{1-6}haloalkyl$;
R^4 is H or $C_{1-4}alkyl$;
X is N, O or S; and
A is OH, NO_2, NH_2 or halo.

3. The compound according to any one of claims 1 or 2 wherein ring P is $C_{6-10}aryl$ and R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}haloalkyl$, $C_{1-6}haloalkylO$, $phenylC_{0-6}alkyl$, $C_{5-6}heteroarylC_{0-6}alkyl$, $C_{3-7}cycloalkylC_{0-6}alkyl$, $C_{3-7}heterocycloalkylC_{0-6}alkyl$, $C_{1-6}alkylOC_{0-6}alkyl$, $C_{1-6}alkylSC_{0-6}alkyl$ or $C_{1-6}alkylNC_{0-6}alkyl$.

4. The compound according to any one of claims 1 or 2 wherein ring P is $C_{5-6}heteroaryl$ and R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}haloalkyl$, $C_{1-6}haloalkylO$, $phenylC_{0-6}alkyl$, $C_{5-6}heteroarylC_{0-6}alkyl$, $C_{3-7}cycloalkylC_{0-6}alkyl$, $C_{3-7}heterocycloalkylC_{0-6}alkyl$, $C_{1-6}alkylOC_{0-6}alkyl$, $C_{1-6}alkylSC_{0-6}alkyl$ or $C_{1-6}alkylNC_{0-6}alkyl$.

5. The compound according to any one of claims 1 or 2 wherein ring P is $C_{6-10}aryl$ fused with phenyl, $C_{5-6}heteroaryl$, $C_{3-7}cycloalkyl$ or $C_{3-7}heterocycloalkyl$ and R^1 is H, NO_2, NH_2, halo, $N(C_{1-6}alkyl)_2$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}haloalkyl$, $C_{1-6}haloalkylO$, $phenylC_{0-6}alkyl$, $C_{5-6}heteroarylC_{0-6}alkyl$, $C_{3-7}cycloalkylC_{0-6}alkyl$, $C_{3-7}heterocycloalkylC_{0-6}alkyl$, $C_{1-6}alkylOC_{0-6}alkyl$, $C_{1-6}alkylSC_{0-6}alkyl$ or $C_{1-6}alkylNC_{0-6}alkyl$.

6. The compound according to any one of claims 1 or 2 wherein ring P is phenyl, pyrazole, pyridine, furan or thiophene.

7. The compound according to any one of claims 1 to 6 wherein R^3 is methyl.

8. The compounds selected from the group consisting of

3-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide,

2-tert-Butyl-5-methyl-2*H*-pyrazole-3 -carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

2-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide,

2-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-3-trifluoromethyl-benzamide,

4-Fluoro-*N*-(2-methyl-benzothiazol-5-yl)-3-trifluoromethyl-benzamide,

3,4-Dimethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid (2-methylbenzothiazol-5-yl)-amide,

N-(2-Methyl-benzothiazol-5-yl)-6-trifluoromethyl-nicotinamide,

N-(2-Methyl-benzothiazol-5-yl)-4-propyl-benzamide,

3-Iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

2,5-Dimethyl-furan-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

N-(2-Methyl-benzothiazol-5-yl)-3-phenyl-propionamide,

5-tert-Butyl-2-methyl-furan-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

4-Bromo-3-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

3,4-Difluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

3-Chloro-2-fluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

Pyridine-2-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

2-Benzyl-5-tert-butyl-2*H*-pyrazole-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

3-Fluoro-4-trifluoromethyl-*N*-(2-trifluoromethyl-1*H*-benzoimidazol-5-yl)-benzamide,

2-Fluoro-5-trifluoromethyl-*N*-(2-trifluoromethyl-1*H*-benzoimidazol-5-yl)-benzamide,

4-Chloro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

1-Phenyl-5-trifluoromethyl-1*H*-pyrazole-3-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

1-Phenyl-5-propyl-1*H*-pyrazole-4-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,

2,3-Difluoro-*N*-(2-methyl-benzothiazol-5-yl)-4-trifluoromethyl-benzamide,

3-Fluoro-4-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

4-tert-Butyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

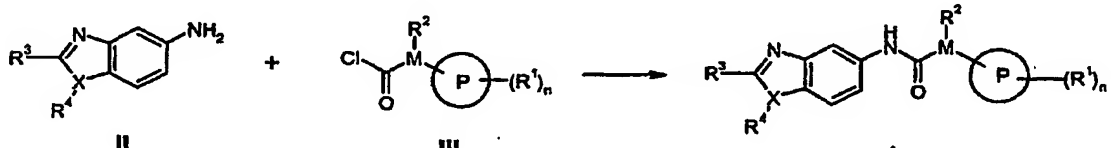
4-Ethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,

N-[1-(2-hydroxyethyl)-2-methyl-1*H*-benzimidazol-5-yl]-*N'*-(4-methoxyphenyl)urea,

N-(3,5-dimethoxyphenyl)-*N'*-[1-(2-hydroxyethyl)-2-methyl-1*H*-benzimidazol-5-yl]urea,
2-(3,4-Difluoro-phenylamino)-*N*-(2-methyl-benzothiazol-5-yl)-acetamide,
4-tert-Butyl-*N*-(2-methyl-benzooxazol-5-yl)-benzamide,
Biphenyl-4-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,
3-Bromo-thiophene-2-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,
4-Bromo-2-methyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-tert-Butoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
2-Chloro-3,4-dimethoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-Iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-Amino-*N*-(2-methyl-benzothiazol-5-yl)-3-nitro-benzamide,
N-(2-Methyl-benzothiazol-5-yl)-4-vinyl-benzamide,
4-Ethoxy-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-Ethylsulfanyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-Dimethylamino-naphthalene-1-carboxylic acid (2-methyl-benzothiazol-5-yl)-amide,
2-Fluoro-6-iodo-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
4-Ethoxymethyl-*N*-(2-methyl-benzothiazol-5-yl)-benzamide,
N-(2-Methyl-benzothiazol-5-yl)-4-trifluoromethoxy-benzamide, and
4-Chloro-3-fluoro-*N*-(2-methyl-benzothiazol-5-yl)-benzamide.
or salts, solvates or solvated salts thereof.

9. A processes for the preparation of the compound according to claim 1, wherein R^1 to R^4, are defined as in claim 1, comprising;

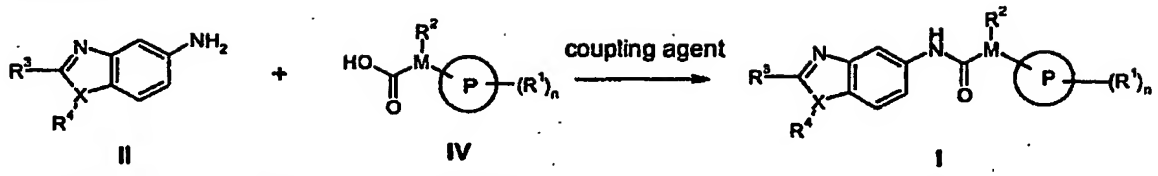
Method A



II III I

whereby the amide of formula I is obtained from the amine of formula II and an appropriate acyl chloride of formula III,
or

Method B



II IV I

whereby the amide of formula I is obtained from the amine of formula II and an appropriate carboxylic acid of formula IV in the presence of a coupling agent.

10. The compound according to any one of claims 1 to 8, for use in therapy.

11. Use of the compound according to any one of claims 1 to 8, in treatment of VR1 mediated disorders.

12. The use according to claim 11 for treatment of acute and chronic pain disorders.

13. The use according to claim 11 for treatment of acute and chronic inflammatory pain.

14. The use according to claim 11 for treatment of indications selected form the group consisting of arthritis, fibromyalgia, low back pain, post-operative pain, visceral pains like chronic pelvic pain, cystitis, IBS, pancreatitis, sciatia, diabetic neuropathy, HIV neuropathy, asthma, cough, IBD, psoriasis, gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder.

15. Use of the compound of formula I according to any one of claims 1 to 8, in the manufacture of a medicament for the treatment of VR1 mediated disorders and for the treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.

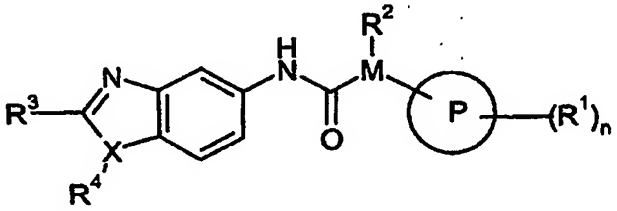
16. A method of treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders and acute and chronic inflammatory pain, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 8.

17. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 8, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

18. The pharmaceutical formulation according to claim 17, for use in the treatment of VR1 mediated disorders and for treatment of acute and chronic pain disorders and acute and chronic inflammatory pain.

ABSTRACT

The present invention relates to new compounds of formula I,



(I)

wherein R^1 to R^4 are as defined as in formula I, or salts, solvates or solvated salts thereof, processes for their preparation, pharmaceutical formulations containing said compounds and to the use of said compounds in therapy.

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